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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,599	11/04/2003	Bernd Bohrmann	21459	6499

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	**PAPER NUMBER**
1655	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,599	BOHRMANN ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/18/04 ,2/9/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending in this application and were examined on their merits.

Claim Objections

Claim 20 is objected to because of the following informalities: "Peptide" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass protein chemistry and immunochemistry methods of isolating β-amyloid from a body fluid and the preparation of that isolated β-amyloid by methods comprising chemical reactions with flight enhancers and chemical fragmentation.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. MPEP § 2163.

Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic.

In re Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe the subgenus. *In re Gostelli*, F.2d at 1012, USPQ2d at 1618.

The instant specification only provides one example of protein chemical and immunochemical methods, no example or description of flight enhancers or the chemical reactions involving them, and only two examples of chemicals having fragmentation capabilities.

As stated *supra*, the MPEP states that the written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable, that Claim 12 and 14 are broad generics, with respect to all possible methods of protein chemistry, immunochemistry, chemical fragmentation and reactions with flight enhancers. The possible structure variations as disclosed in the specification are limitless, and examples reflecting the variety of possible species in the genus are not provided.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 uses improper Markush language, in the third line where it states, "...selected from the group comprising...". It could be corrected, for example, by changing "comprising" to "consisting of".

Claim 18 recites the "...with the help of the base-line separation..." It is unclear whether or not this constitutes another method step. If so, correction is required.

Claim 20 recites the limitation "in body fluid" in the second line of the claim. There is insufficient antecedent basis for this limitation in the claim because Claim 18 is limited to mammalian brain tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-13, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bougneres *et al.* (1982) in view of Kametani *et al.* (1999).

Bougneres *et al.* teaches a method for the quantification of palmitate by providing a source of palmitate (blood plasma), adding a defined amount of palmitate labeled with a stable isotope (H^2 and/or C^{13}) to the source (Pg. 502, Column 1, Lines 1-12), isolating the labeled and unlabeled palmitate (Pg. 503, Column 1, Lines 43-52 and Column 2, Lines 1-21), desalting the sample to be analyzed (Pg. 503, Column 2, Lines 7-9), analyzing the prepared palmitate by mass spectroscopy (Pg. 503, Column 2, Lines, 21-26) and determining the amount of palmitate that was present in the source of palmitate using base-line separation (Pg. 504, Column 1, Lines 25 and Column 2, Lines 1-28).

Bougneres *et al.* does not teach the use of the method with aggregated, soluble β-amyloid peptides obtained from the source of a tissue sample (mammalian brain) (obtained through laser dissection excision) or body fluid, wherein the β-amyloid peptides are either amino or carboxy terminal microheterogenous.

Bougneres *et al.* does not teach the method of isolation from a body fluid using protein chemistry and immunochemistry, or from a tissue sample comprising dissolution with solubilizing agents.

Bougneres *et al.* does not teach the preparation for analysis by mass spectroscopy by methods comprising chemical reactions with flight enhancers, chemical fragmentation, and enzymatic digestion by a protease.

Bougneres *et al.* does not teach the method of using MALDI-TOF mass spectroscopy.

Bougneres *et al.* does not teach a method wherein the labeled palmitate has been either synthetically or recombinantly produced.

Kametani *et al.* teaches a method for the semiquantitation of amyloid-β (amino terminal and carboxy terminal) peptides (Pg. 262, Column 2, Lines 3-6 and 49-50) wherein a source of aggregated β-amyloid is obtained from a homogenized brain tissue sample (Pg. 264, Fig.3), an anti-β-amyloid antibody is added, and the precipitated antibody-β-amyloid complex is analyzed using Matrix-Assisted Laser Desorption Ionization/Time-Of-Flight-Mass Spectroscopy (MALDI-TOF) (Pg. 263, Fig. 1)

Kametani *et al.* teaches the preparation for analysis of the isolated β-amyloid by chemical fragmentation and dissolution in a solubilizing agent. (Pg.262, Column 2, Lines 37-46).

One of ordinary skill in the art at the time of the invention would have been motivated to combine the method of Bougneres *et al.* with the method of Kametani *et al.* because Isotope Dilution is well known as an accurate and definitive and is capable of being used without the use of unstable radioactive tracers as well enabling the measurement of a internal standard simultaneously with the element of interest. The ordinary artisan at the time of invention would have known that the Gas/Liquid Chromatography-Mass Spectrometry (GLC/MS) technique used by Bougneres is not sensitive enough to detect the β-amyloid peptide of interest, and the more sensitive method of Matrix Assisted Laser Desorption Ionization/Time-of-flight-Mass Spectrometry (MALDI-TOF) would be better suited. The ordinary artisan would have had a reasonable expectation of success in combining the two methods because both techniques are well documented in the art and were used successfully individually.

Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bougneres *et al.* (1982), in view of Kametani *et al.* (1999) as applied to claims 1, 5-13,16 and 17 above, and further in view of Schutze *et al.* (1998).

The teachings of Bougneres *et al.* (1982) and Kametani Bougneres *et al.* (1999) were discussed *supra.*

Schutze *et al.* teaches the use of laser dissection microscopy to capture samples of any shape and size including cell clusters and single cells. (Pg. 737, Column 1, Lines 38-40 and Column 2, Lines 1-2).

The ordinary artisan would have been motivated to modify the methods of Bougneres *et al.* and Kametani *et al.* with the addition of the laser dissection microscopy technique because the high degree of accuracy over conventional dissection methods would enable the artisan to excise more completely those minute areas of tissue containing β-amyloid to be examined with less contamination from surrounding tissue and maintain the integrity of the tissue section. As the technique had been practiced with success by other Researchers, the ordinary artisan would have had a reasonable expectation of success in combining this technique with those of Bougneres *et al.* and Kametani *et al.*

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bougneres *et al.* (1982), in view of Kametani *et al.* (1999) as applied to claims 1, 5-13, and 16-22 above, and further in view of Nyman *et al.* (1998).

The teachings of Bougneres *et al.* (1982) and Kametani *et al.* (1999) were discussed *supra.*

Nyman *et al.* teaches the use of the preparation of samples for MALDI-TOF mass spectroscopy by enzymatic digestion with Endoproteinases Lys-C and Glu-C. (Pg. 296, Column 2, Lines 36-48 and Pg. 299, Table 2).

The ordinary artisan at the time of the instant invention would have been motivated to use enzymatic digestion to break down the constituent proteins of the β-amyloid samples into peptides of a size capable of analysis by MALDI-TOF. The ordinary artisan would have had a reasonable expectation of success because the technique had been used before with success by Nyman *et al.* in examining other proteins.

Claims 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bougneres *et al.* (1982), in view of Kametani *et al.* (1999) as applied to claims 1, and 5-22 above, in view of Nyman *et al.* (1998), and further in view of Wang *et al.* (1996).

The teachings of Bougneres *et al.* (1982), Kametani *et al.* (1999) and Nyman *et al.* (1998) were discussed *supra.*

Wang *et al.* teaches the isolation and quantification of synthetic and recombinant β-amyloid peptide by immunoprecipitation, the preparation for analysis by mass spectroscopy (MALDI-TOF) using flight enhancers and chemical fragmentation. (Pg. 31895, Lines 14-75)

It would have been obvious to one of ordinary skill in the art to use synthetic and/or recombinant β-amyloid peptide because this would enable the artisan to control what isotopes were incorporated as labels and provide β-amyloid peptide in large amounts not available by any other method. The ordinary artisan with skill in the art of MALDI-TOF Mass Spectrometry would have been well acquainted with the processing of protein samples by chemical fragmentation and the use of flight enhancers to increase the intensities of MALDI-TOF MS signals of peptides for greater accuracy.

Based on the success of Wang *et al.* the ordinary artisan would have had a reasonable expectation of success in combining this method with the methods taught by the references above.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one with ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence or evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Paul Martin
Examiner
Art Unit 1655

11/08/05

PATRICIA LEITH
PRIMARY EXAMINER